--45. (New) A method of producing a CD4-gamma2 chimeric heavy chain homodimer which comprises:

a) transfecting a eukaryotic cell with the expression vector of claim 44;

b) culturing the resulting transfected mammalian cell under conditions such that chimeric heavy chain homodimer is produced; and

c) recovering the chimeric heavy chain homodimer so produced.--

E2 cont.

--46 A method of claim 45, wherein the eukaryotic cell is a COS cell, CHO cell or myeloma cell.--

add G'

REMARKS

Claims 30-35 and 43 are pending in this application. By this Amendment, applicants have amended claim 30, cancelled claim 43 without prejudice and added new claims 44, 45 and 46 which correspond to the original claims 1, 3 and 4. Support for the amended claim 30 may be found inter alia on page 34. Accordingly there is no issue of new matters and applicants respectfully request the entry of this Amendment. Upon entry claims 30-35 and 44-46 are under examination. In a January 8, 1997 telephone conference between the undersigned attorney and Examiner Brown, the Examiner stated that new claims 44-46 will be examined if they are added into this application.

Sequence Listing

The Examiner stated that this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.82(a)(1) and (a)(2). The Examiner stated that this application fails to comply with the requirements of CFR 1.821 through 1.825 for the reasons(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The Examiner stated that the

specification contains oligonucleotide sequences at least at pages 32, 41, and 43, and Figures 1B and 3-5 include nucleotide and/or amino acid sequences which must have sequence identifiers listed in a Sequence Listing.

In response, applicants submit hereto as Exhibit A, a paper copy of the Sequence Listing, a computer disk which contains the computer readable form of the Sequence Listing information and a statement declaring the sequence information on the disk is the same as the paper copy (Exhibit B). Applicants have also made appropriate amendments to the specification to add the ID identifiers. Accordingly, applicants believe that the requirements of CFR 1.821 through 1.825 have been fully satisfied.

Drawings

The Examiner stated that each page of Figures 3-5 must have a separate part number (e.g. 3A, 3B, 3C, etc.), and the Brief Description of the Drawings must be amended to recite the different part numbers of the drawings.

In response, applicants will make the appropriate changes of the Figures and therefore the specification when this application is placed in condition for allowance.

Specification

The Examiner stated that the disclosure is objected to because of the following informalities; On page 19, at lines 2-9, the specification states that expression vector CD4-IgG2-pcDNA1 is deposited under ATCC Accession No. 40952, while at line 14, the specification states that the same expression vector is deposited under ATCC Accession No. 40951. The Examiner required appropriate clarification and correction.

In response, applicants have hereinabove amended the specification to recite the correct ATCC No. of the expression vector CD4-IgG2-pcDNA1 which is 40952. Applicants believe that this Amendment

should obviate this ground of rejection.

Claim Rejections - 35 USC §112

The Examiner rejected claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

In response, applicants have hereinabove cancelled claim 43 thereby rendering this rejection moot.

Claim Rejections - 35 USC §103

The Examiner rejected claims 30-35 and 43 under 35 U.S.C. 103(a) as being unpatentable over Capon, et al. (U.S. Pat. No. 5,565,335).

The Examiner stated that '335 discloses immunoglobulin fusion proteins comprising CD4 and to the C-terminal Fc portion of an antibody, which Fc region consists of the hinge, CH2 and CH3 domains of the heavy chain of an IgG and which contains the intermolecular disulfide bond region of the hinge domain (col. 7, lines 50-64, and col. 26, line 44 to col. 28, line 14). The Examiner further stated that '335 also discloses that CD4 fused to the constant domain of an IgG heavy chain results in secretion of a CD4-IgG homodimer. The Examiner stated that '335 also teaches a CD4-IgG heterotetramer composed of two CD4-light chain fusion proteins and two CD4-heavy chain fusions (col. 6, line 61 to col. 7, line 11) and discloses that suitable fusion proteins can be obtained from IgG-1, -2, -3 or -4, as well as IgA, IgE, IgD or IgM (col. 7, lines 47-49). The Examiner stated that '335 further teaches that the CD4-IgG fusion protein can be conjugated to toxins such as deglycosylated ricin A chain or Diptheria toxin (col. 8, line 62 to col. 9, line 7). The Examiner stated that '335 discloses that CD4-IgG fusion proteins can be used in compositions to treat HIV (col. 1, lines 11-15) or can be labeled for use as a diagnostic reagent (col. 10, line 66 to col. 11, line 4). Although '335 does not exemplify a CD4-IgG2 fusion protein, as claimed in

the instant application, it would have been obvious to one having ordinary skill in the art at the time the invention was made to follow the teachings and motivations of '335 to make any CD4-IgG homodimer, including the claimed CD4-IgG2 homodimers, heterotetramers, as well as conjugates thereof. The Examiner further stated that the skilled artisan would have had a reasonable expectation of success that a CD4-IgG2 homodimer would be biologically active because the constant domains of IgG proteins are similar to one another and because '335 teaches that any IgG subtype can be used in the CD4-IgG fusion. The Examiner stated that although Applicants state that the CD4-IgG2 homodimers would be less likely to increase infection of monocytes/macrophages by HIV than CD4-IgG1 when administered *in vivo*, the specification provides no *in vivo* or *in vitro* evidence that CD4-IgG2 has these properties. Thus, the change of IgG1 in the CD4-IgG fusion to IgG2 is considered *prima facie* obvious, since a minor change in the chemical configuration of a molecule is considered to be *de minimis*, and is not deemed to impart any patentable differences, absent evidence to the contrary (*Ex parte Anderson* 30 USPQ2d, 1866).

In response, applicants respectfully traverse the Examiner's position that a *prima facie* case of obviousness has been established. M.P.E.P. § 2143 (Rev.2, July 1996) states: "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference.... Second, there must be a reasonable expectation of success." and finally, "the prior art reference (or references when combined) must teach or suggest all the claim limitations." (Copies of this and subsequently cited M.P.E.P. sections are attached hereto as Exhibit C). Applicants respectfully submit that none of these three requirements have been met for the reasons that follow.

The Examiner admitted that "'335 [Capon et al.] does not exemplify

a CD4-IgG2 fusion protein..." but alleged that "it would have been obvious ... to make any CD4-IgG homodimer, including the claimed CD4-IgG2 homodimers...." However, there is no close structural similarity between the polypeptide recited in the claims and the polypeptides disclosed in Capon et al. None of the polypeptides recited in Capon et al. have the requisite close structural similarity to applicants' compound. Thus, a *prima facie* case of obviousness does not exist, and an obviousness rejection should not be maintained.

To establish a *prima facie* case of obviousness of a compound, the Office must establish that close structural similarity exists between the claimed compound and those disclosed in the prior art. M.P.E.P. §2144.09 (Rev. 2 July 1996). No such close structural similarity exists between applicants' claimed compound and those disclosed by the prior art.

Whether or not Capon et al. provide the methodology for producing applicants' claimed invention is not a proper basis for a determination that a *prima facie* case of obviousness exists. That a "claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish a *prima facie* case of obviousness." M.P.E.P. §2143.01 (Rev.2, July 1996). Moreover, 35 U.S.C. §103(a) in the concluding sentence states "patentability shall not be negatived by the manner in which the invention was made." Therefore, an obviousness rejection should not be maintained on the basis that Capon et al. may provide the methodology for producing a compound similar to the applicants' claimed invention.

More importantly, Capon et al. do not teach or suggest applicants' claimed polypeptide or a polypeptide having close structural similarity to it. Yet, such a teaching or suggestion must appear in the cited reference to satisfy a basic requirement of a *prima facie* case of obviousness. M.P.E.P. §2143, citing In re Vaeck 947 F.2d 488 (Fed. Cir. 1991).

Applicants' claimed compound is specific. There is no suggestion or motivation in Capon et al. to change their disclosed molecules in the manner to the specific compound claimed by applicants. The fact that the Capon et al. molecules and the claimed molecule have some amino acids in common does not make them structural homologs.

Additionally, one skilled in the art would not have had a reasonable expectation of success with respect to the claimed polypeptide because of unpredictability in the art. The chemical divergence is enormous and the range of possibilities is huge. There are millions of possible modifications, including not only deletions but also substitutions, additions and so on. Such an overwhelming number of possibilities is simply inconsistent with close structural similarity.

In other words, absent applicants' disclosure, an ordinary skilled artisan at the time of applicants' invention would not have known and not have been motivated to make the specific changes of the fragment taught by Capon et al. to arrive at the specific polypeptide claimed by the applicants. A *prima facie* case requires that one skilled in the art be motivated to arrive at the specific compound prior to introduction of the applicants' teachings.

In conclusion, with respect to the polypeptide recited in the claims, Capon et al. do not provide a suggestion to modify the polypeptides disclosed to the claimed polypeptide. Also, Capon et al. do not provide a reasonable expectation of success as to the activity of the resulting polypeptide. And clearly, as admitted by the Examiner, Capon et al. do not teach the specific polypeptide.

Accordingly, in view of the foregoing, applicants respectfully request that the Examiner reconsider and withdraw the restriction requirement.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned

attorney invites the Examiner to telephone at the number provided below.

No fee, other than the $465.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of Amendment. Applicants have enclosed herein a check in the amount of $465.00 to cover this fee. However, if any additional fee is required, authorization is hereby given to charge the amount of any such additional fee to Deposit Account No. 03-3125.

Respectfully submitted,

Albert Wai Kit Chan

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Albert Wai-Kit Chan 5/13/97
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